ANTICANCER RESEARCH *42*: 4189-4197 (2022)
doi:10.21873/anticanres.15919

Review

Craniopharyngiomas Invading the Ventricular System: A Systematic Review

PAOLO PALMISCIANO[1], KURTIS YOUNG[2], MAYA OGASAWARA[3], OMID YOUSEFI[4], CHRISTIAN OGASAWARA[5], GIANLUCA FERINI[6], OTHMAN BIN-ALAMER[7], MAYUR SHARMA[8], GIUSEPPE E. UMANA[9], KENNY YU[10], AARON A. COHEN-GADOL[11], TAREK Y. EL AHMADIEH[10] and ALI S. HAIDER[12]

[1]*Department of Neurosurgery, University of Cincinnati College of Medicine, Cincinnati, OH, U.S.A;*
[2]*John A. Burns School of Medicine, University oh Hawai'i, Honolulu, HI, U.S.A.;*
[3]*University of California, Berkeley, CA, U.S.A.;*
[4]*Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran;*
[5]*Department of Neurosurgery, University of Texas Medical Branch, Galveston, TX, U.S.A.;*
[6]*Department of Radiation Oncology, REM Radioterapia srl, Viagrande, Italy;*
[7]*Department of Neurosurgery, University of Pittsburgh Medical Center, Pittsburgh, PA, U.S.A.;*
[8]*Department of Neurosurgery, University of Louisville, Louisville, KY, U.S.A.;*
[9]*Department of Neurosurgery, Trauma Center, Gamma Knife Center, Cannizzaro Hospital, Catania, Italy;*
[10]*Department of Neurosurgery, Memorial Sloan Kettering Cancer Center, New York, NY, U.S.A.;*
[11]*Department of Neurological Surgery, Indiana University School of Medicine, Indianapolis, IN, U.S.A.;*
[12]*Department of Neurosurgery, The University of Texas M.D. Anderson Cancer Center, Houston, TX, U.S.A.*

Abstract. *Background/Aim: Craniopharyngiomas involving the ventricular system are rare but pose significant surgical challenges. We systematically reviewed the literature on craniopharyngiomas invading the ventricles (CP-V). Materials and Methods: PubMed, EMBASE, Scopus, Web of Science, and Cochrane were searched to include studies reporting clinical data of patients with CP-Vs. Clinico-radiological features, management, and treatment outcomes were analyzed. Results: We included 73 studies encompassing 407 patients. Patients were mostly male (61.5%), presenting with headache (57.9%) and/or endocrine disorders (52.1%). CP-Vs mostly involved the third ventricle (96.3%), followed by the lateral ventricles (2.9%), and the fourth ventricle (1%). Tumors had cystic components in 59% of cases and were mostly adamantinomatous (70.8%). Open resection was performed in 232 cases (57%), mostly with trans-lamina terminalis (36.6%) and trans-callosal (31.9%) approaches. Endoscopic resection was performed in 169 cases (41.5%), mostly with trans-sphenoidal (74.6%) and trans-ventricular (24.9%) approaches. Gross-total tumor resection was obtained in most cases (62.9%). Adjuvant radiotherapy was delivered in 22.8% cases. A total of 178 patients experienced persistent complications, mostly including diabetes insipidus (47.1%) and panhypopituitarism (12.7%), not significantly different after open versus endoscopic resection (p=0.117). Symptom improvement was obtained in 88% of cases. CP-Vs recurrences were reported in 94 patients (23.1%), with median progression-free survival of 13.5 months (range=0.5-252.0 months). Fifty-nine patients died (14.5%), with median overall survival of 32.0 months (range=0.5-252.0 months), significantly longer after endoscopic resection than open resection (p=0.019). Conclusion: CP-Vs are uncommon and challenging entities. Surgical resection is feasible, but patient-tailored selection of open/endoscopic approaches is necessary to achieve optimal outcomes and minimize complication risks.*

Correspondence to: Paolo Palmisciano, MD, Department of Neurosurgery, University of Cincinnati College of Medicine, 231 Albert Sabin Way, 45229 Cincinnati, OH, U.S.A. Tel: +1 5139188419, e-mail: paolo.palmisciano94@gmail.com

Key Words: Cerebral ventricles, craniopharyngioma, intraventricular tumor, neuro-oncology, skull base, systematic review.

This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY-NC-ND) 4.0 international license (https://creativecommons.org/licenses/by-nc-nd/4.0).

Craniopharyngiomas comprise a heterogeneous group of benign neoplasms accounting for 1.2-4.6% of all intracranial tumors and showing two peaks of age incidence, in children or young

adolescents (5-15 years) and in middle-age adults (45-60 years) (1, 2). Craniopharyngiomas are presumed to originate from the cell remnants of the craniopharyngeal duct (*i.e.*, Rathke's pouch) within the pars tuberalis, which migrate upward during hypophysis-genesis into close contact with the infundibulum-tuber cinereum (3, 4). This embryological origin explains the location of craniopharyngiomas within the sellar/suprasellar regions, with classical clinical presentation characterized by endocrine and/or visual impairments (5). Brain magnetic resonance imaging (MRI) assists the pre-operative differential diagnosis, and current treatment strategies primarily include surgical tumor resection, with or without ventricular shunting, and/or upfront or adjuvant radiotherapy (6).

Due to their origin along the hypothalamic-pituitary axis, craniopharyngiomas may involve the ventricular system (7). In particular, infundibulo-tuberal craniopharyngiomas comprise tumors originating at the floor of the third ventricle (8), which may extend into the ventricular cavity after breaking through the ependyma, while the "strictly third-ventricular craniopharyngiomas" define subependymal tumors growing exclusively within the third ventricle (9). In rarer cases, craniopharyngiomas may invade the lateral ventricles (10) and/or occur at the cerebellopontine angle with involvement of the fourth ventricle (11). The surgical and/or radiation management of these tumors appears particularly difficult due to their close relationship with the hypothalamic system and critical neurovascular structures, with significant risks of severe post-treatment complications and major impairment of patient's quality of life (4).

Recently, Prieto *et al*. (9) systematically reviewed studies reporting strictly third-ventricular craniopharyngiomas, but they excluded craniopharyngiomas secondarily invading the ventricular system, which characterize challenging entities whose management remains unclear. In this systematic review, we comprehensively summarized the literature on clinico-radiological presentation, treatment strategies, and outcomes in all patients with craniopharyngiomas involving the ventricular system (CP-Vs).

Materials and Methods

Literature search. A systematic review was performed upon the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (12). PubMed, EMBASE, Scopus, Web of Science, and Cochrane were searched from inception to May 25, 2022, using the combination of the Boolean operators "OR" and "AND" and the search terms: "ventricle*", "intraventricular", and "craniopharyngioma*". Studies were exported to Mendeley, and duplicates were removed.

Study selection. Inclusion and exclusion criteria were defined a priori. Studies were included if they: 1) involved ≥1 patients with histologically confirmed craniopharyngiomas involving the ventricular system, as reported by the authors; 2) reported data on clinical characteristics, treatments, outcomes; 3) were written in English. CP-Vs were defined as craniopharyngiomas developing subependimally and exclusively within the ventricular system (*i.e.*, strictly intraventricular craniopharyngiomas) and/or craniopharyngiomas originating below the floor of the third ventricle (*i.e.*, infundibulo-tuberal) and extending into the ventricular system. Studies were excluded if they were: 1) literature reviews, autopsy reports, conference abstracts, videos, editorials, or books; 2) studies with unclear distinction between patients with CP-Vs and patients with different tumors or with craniopharyngiomas not involving the ventricles.

Two reviewers (P.P. and C.O.) independently screened titles and abstracts of all collected studies, and then assessed full texts of articles that met inclusion criteria. A third reviewer (A.S.H.) settled any disagreements at both stages of screening. Eligible studies were included based on the predefined criteria and references were screened to retrieve additional relevant articles.

Data extraction. Data were extracted by three reviewers (K.Y., M.O., and O.Y.) and then confirmed by one additional reviewer (P.P.). Missing data were not reported by the authors. Extracted data included: authors, year, sample size, age, sex, presenting symptoms, ventricle involved, radiological appearance, histological features, surgical approach, extent of surgery, adjuvant radiotherapy, post-treatment complications, clinical improvement, recurrence, progression-free survival (PFS), overall survival (OS), survival status. Extent-of-surgical resection was defined as gross total resection (GTR) for 100% tumor resection, subtotal resection (STR) for 80-99% resection, and partial resection (PR) for <80% resection. Complications were divided into "transient", if self-resolving or treated with only medical therapy, and "persistent", if untreatable or requiring re-operation. Clinical improvement was assessed at last available follow-up and was defined as improvement in symptoms (*e.g.*, vision disturbances and/or endocrine deficits) reported at baseline pre-treatment evaluation.

Data synthesis and quality assessment. The primary outcomes of interest were the clinico-radiological features, management, and post-treatment outcomes of patients with CP-Vs. For each article, level of evidence was appraised in accordance with the 2011 Oxford Centre For Evidence-Based Medicine guidelines (13). A study-level meta-analysis was precluded because all included studies had levels IV of evidence and hazard ratios could not be deducted. However, individual patient data were extracted for individual patient data meta-analyses (14). Risk of bias of each study was independently evaluated by two reviewers (P.P. and C.O.) using the JBI checklist (15). The overall risk of bias for this review was determined by considering the risk of bias of all included studies in aggregate.

Statistical analysis. SPSS V.25 (IBM Corp, Armonk, NY, USA) was used for all statistical analyses and a two-tailed p-value <0.05 was considered significant. Continuous variables are reported as medians and ranges, while categorical variables as frequencies and percentages. The Chi-square test was used to compare complication rates after open *versus* endoscopic tumor resection. The time intervals between surgery and recurrence (PFS curve) or death (OS curve) were estimated using the Kaplan–Meier method, and the survival analyses were conducted using the log-rank test.

Results

Study selection and overview. The initial search yielded 2,409 citations (PubMed: 640; EMBASE: 939; Scopus: 595;

Table I. *Summary of clinico-radiological features of all pooled patients.*

Characteristics	Value
Cohort size (no.)	407
Demographics	
Age (years), median (range) (n=388)	45 (1.5-84.0)
Sex (male) (n=378)	232 (61.4%)
Presenting symptoms (n=390)	No. (%)
Headache	226 (57.9%)
Endocrine disorders	203 (52.1%)
Hydrocephalus	183 (46.9%)
Visual acuity impairment	181 (46.4%)
Intracranial hypertension (headache, vomit, papilledema)	158 (40.5%)
Panhypopituitarism	52 (13.3%)
Confusion/ Cognitive decline	30 (7.7%)
Bitemporal hemianopsia	24 (6.2%)
Memory disturbance	20 (5.1%)
Altered consciousness	18 (4.6%)
Incontinence	7 (1.8%)
Cranial nerve VI palsy	6 (1.5%)
Quadrantopsia	3 (0.8%)
No symptoms	3 (0.8%)
Ventricle involved	No. (%)
Third	392 (96.3%)
Lateral	12 (2.9%)
Fourth	4 (1%)
Radiological appearance (n=178)	No. (%)
Cystic components	105 (59%)
Solid	73 (41%)
Calcified	24 (13.5%)
Histological features (n=192)	No. (%)
Adamantinomatous	136 (70.8%)
Papillary	56 (29.2%)

Table II. *Summary of treatment strategies and outcomes of all pooled patients.*

Characteristics	Value
Surgical management	No. (%)
Open	232 (57%)
Trans-lamina terminalis	85 (36.6%)
Trans-ventricular	74 (31.9%)
Trans-callosal	57 (24.6%)
Trans-cortical	12 (5.2%)
Posterior fossa	4 (1.7%)
Endoscopic	169 (41.5%)
Trans-sphenoidal	126 (74.6%)
Trans-ventricular	42 (24.9%)
Trans-cortical	1 (0.5%)
Combined (open & endoscopic)	6 (1.5%)
Trans-ventricular	5 (100%)
Extent of surgery	No. (%)
Gross-total (90-100%)	256 (62.9%)
Subtotal (80-90%)	66 (16.2%)
Partial (<80%)	83 (20.4%)
Biopsy	2 (0.5%)
Adjuvant radiotherapy (n=351)	80 (22.8%)
Complications (n=378)	No. (%)
Transient	27 (7.1%)
Diabetes insipidus	26 (6.9%)
Mutism	1 (0.2%)
Persistent	178 (47.1%)
Diabetes insipidus	102 (27%)
Panhypopituitarism	48 (12.7%)
Cerebrospinal fluid leak	23 (6.1%)
Meningitis	11 (2.9%)
Symptom improvement (n=350)	308 (88%)
Recurrence	94 (23.1%)
Survival	
Follow-up (months), median (range)	32.0 (0.5-252.0)
Progression free survival (months), median (range)	13.5 (0.5-252.0)
Overall survival (months), median (range)	32.0 (0.5-252.0)
Status	No. (%)
Alive	348 (85.5%)
Dead	59 (14.5%)

Web of Science: 233; Cochrane: 2) (Supplementary File 1). A total of 30 case series and 43 case reports were finally included, categorized as level IV and V of evidence (Supplementary File 2). Critical assessment returned low risk of bias for all included articles (Supplementary File 3), predisposing this review to a low overall risk of bias.

Demographics and clinico-radiological characteristics. Table I summarizes the demographics and clinico-radiological features of all 407 included patients. Patients were mostly male (61.4%) with a median age of 45 years (range=1.5-84 years). Patients most commonly presented with headache (57.9%), endocrine disorders (52.1%), hydrocephalus (46.9%), and visual acuity impairment (46.4%), with 158 patients experiencing intracranial hypertension (40.5%). Xu *et al*. (16) reported 3 asymptomatic patients who were diagnosed incidentally with CP-Vs at imaging follow-ups. All tumors were suprasellar and mostly involving the third ventricle (96.3%), while 12 tumors (2.9%) involved the lateral ventricle and 4 (1%) involved the fourth ventricle. At imaging, 59% of tumors showed cystic components and 13.5% were partly calcified. Among patients with available histopathological data, 136 tumors were adamantinomatous (70.8%), and 56 were papillary (29.2%).

Treatment strategies. Management strategies are reported in Table II. Patients mostly underwent open tumor resection (57%), followed by endoscopic resection (41.5%), or combined open and endoscopic resection (1.5%). Among patients undergoing open tumor resection, the trans-lamina terminalis approach was the most used (36.6%), followed by trans-ventricular (31.9%), trans-callosal (24.6%), and trans-cortical (5.2%) approaches. Posterior fossa approaches were performed in 4 patients (1.7%) with CP-Vs involving the fourth ventricle

(17-20). Among patients undergoing endoscopic tumor resection, the trans-sphenoidal approach was the most used (74.6%), followed by trans-ventricular (24.9%), and trans-callosal (0.5%) approaches. As regards the extent of tumor resection, GTR, STR, and PR were performed in 62.9%, 16.2%, and 20.4% patients, respectively. Post-surgical adjuvant radiotherapy was delivered in 80 patients (22.8%). Sharma *et al*. (21) and Davies *et al*. (22) reported 2 patients undergoing tumor biopsy with aspiration of the cystic component.

Outcomes, complications, and survival. Table II summarizes outcomes and complications. Patients were followed-up for a median of 32.0 months (range=0.5-252.0 months). Post-treatment symptom improvement occurred in 88% cases. Transient complications were described in 27 patients (15.8%), including new self-resolving diabetes insipidus (6.9%) and mutism (2.9%), with no significant differences after open *vs*. endoscopic tumor resection (p=0.511). Persistent complications were reported in 178 patients (47.1%), mostly new untreatable diabetes insipidus (27%) and hypopituitarism (12.7%), with no significant differences after open *vs*. endoscopic tumor resection (p=0.117). A total of 23 patients (6.1%) experienced cerebrospinal fluid (CSF) leak requiring surgical revision. CP-Vs recurrences were reported in 94 patients (23.1%), with a median PFS of 13.5 months (range=0.5-252.0 months). Most patients were alive at last follow-up (85.5%), with median OS of 32.0 months (range=0.5-252.0 months). The log-rank tests showed that OS was significantly higher only in patients undergoing endoscopic tumor resection compared to patients undergoing open tumor resection (p=0.019) (Figure 1).

Discussion

CP-Vs are uncommon entities characterized by debilitating clinical presentation, complex surgical management, and high risks of negative impact on long-term patient's functional status. Current treatment strategies primarily focus on relieving life-threatening symptoms, especially in patients with intracranial hypertension and/or severe endocrine/vision impairments, but related complications should be considered on a case-by-case basis. In this review, we present a comprehensive summary of the current literature on CP-Vs, further analyzed within the context of the most common craniopharyngiomas not involving the ventricular system.

CP-Vs comprise a broad group of tumors with variable degrees of involvement of the ventricular system. Although some authors have tried to define distinct categories of intraventricular craniopharyngiomas, mostly referring only to the third ventricle, a standardized and universally accepted classification is currently lacking (7-9). These tumors are largely heterogeneous and often present with few overlapping imaging features, posing many difficulties in accurately categorizing each individual case on routine clinical settings (23). By analyzing all these lesions into a single category of craniopharyngiomas extending into the ventricular system, we aim to inform specialists about the most common clinical presentations and available therapeutic options with related outcomes, which may provide valuable information for optimizing patient-tailored treatment planning.

The origin of CP-Vs remains unclear. The involvement of the third ventricle may derive from craniopharyngioma's development along the migration of the Rathke's pouch close to the infundibulum and attached to the third ventricle floor, or from residual squamous epithelium of the stomodeum embedded within the ventricular system at early stages of pituitary gland development (24). Aggressive growth may also lead to tumor's invasion into the lateral ventricles through the Monro's foramina, with only 12 cases reported in the current literature (25-29). A total of 4 cases of fourth ventricle CP-Vs were described, defined as ectopic craniopharyngiomas invading the cerebellopontine angle (11, 18-20), with some authors suggesting a potential relationship with Gardner's syndrome (30). From a histological perspective, adamantinomatous CP-Vs were more common than papillary CP-Vs, in line with the overall craniopharyngioma population (6). The rarity of CP-Vs makes difficult to clearly differentiate their origin as compared to the most common non-ventricular craniopharyngiomas. Detailed genetic and molecular analyses may be warranted to define unique differences of these entities and evaluate the embryogenic role of paracrine cell interactions between Rathke's pouch and craniopharyngioma's precursors, with the goal to identify potential therapeutic targets (31, 32).

As found in this cohort, CP-Vs share similar demographic characteristics with the overall craniopharyngioma's population, prevalent in male patients and peaking in children/adolescents or in middle-age adults (33). The variability in clinical presentation primarily reflects tumor's location within the suprasellar region, with impairment of the endocrine hypothalamic-pituitary axis and/or optic pathways, and within the ventricular cavities, with frequent obstruction of the Monro's foramina and consequent hydrocephalus and/or increased intracranial pressure. These non-specific symptoms are largely similar to the other non-ventricular craniopharyngiomas, showing higher rates of early diagnoses in case of tumors causing intracranial hypertension and more frequent late diagnoses in case of lesions causing progressive hormone and/or visual disturbances (5, 34). In the rare events of fourth ventricle and/or cerebellopontine CP-Vs, the clinical presentation may also include typical cerebellar symptoms in addition to hydrocephalus with intracranial hypertension, making the diagnosis of CP-Vs even more difficult (11, 17).

Advances in imaging techniques have led to higher rates of pre-operative CP-Vs diagnoses in recent years as compared to historic cohorts of tumors diagnosed only intra-operatively or at post-mortem autopsy (9, 35). Imaging

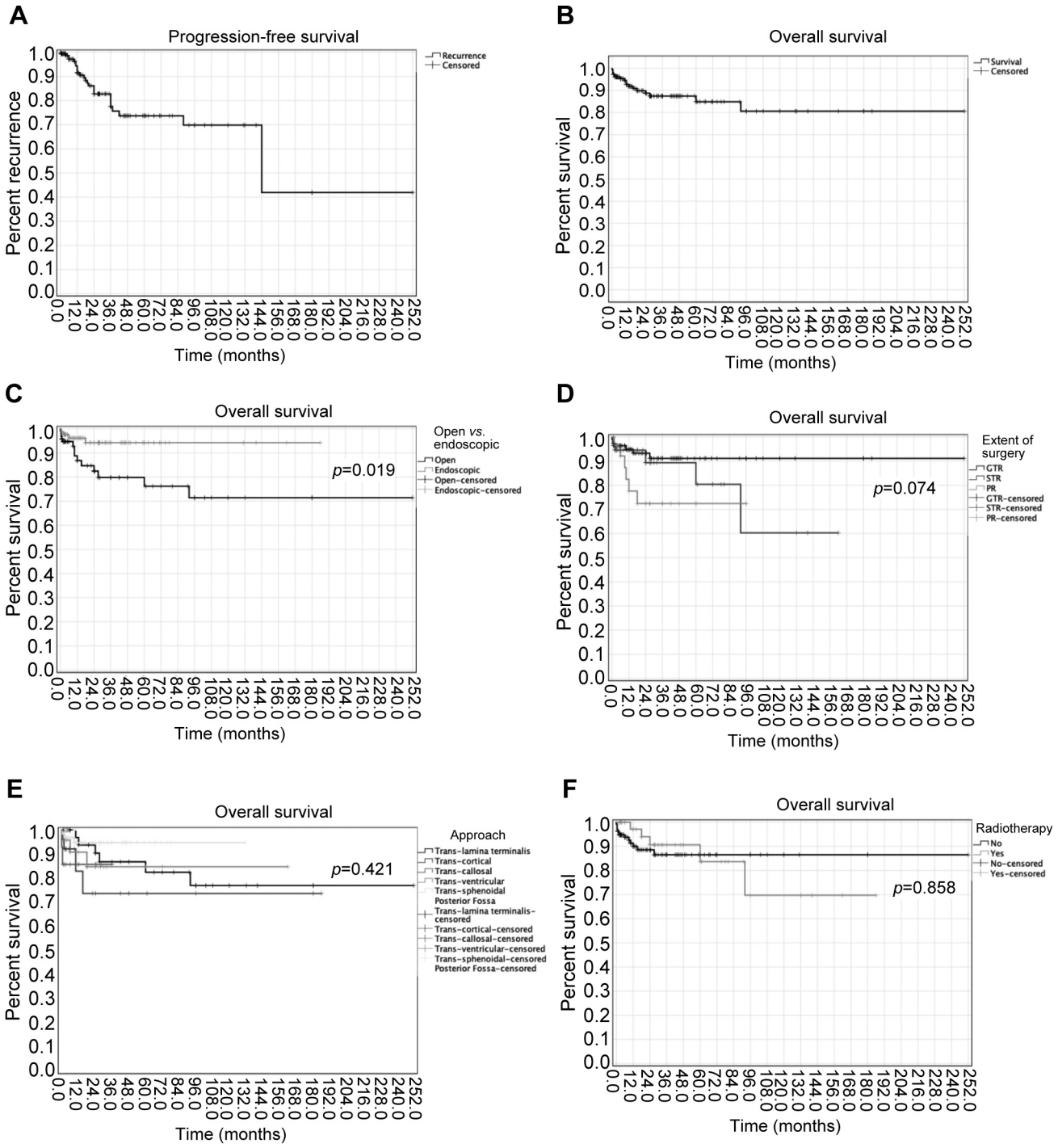

Figure 1. *Kaplan–Meier survival curves of patients with available individual data: (A) progression-free survival and (B) overall survival of the total pooled cohort; overall survival based on (C) open vs. endoscopic surgery, (D) extent of surgery, (E) surgical approach, (F) adjuvant radiotherapy.*

features of CP-Vs are largely similar to those of non-ventricular craniopharyngiomas, frequently characterized by solid parts with or without cystic components and in some cases presenting with intratumor calcifications (36). Although these features may support non-ventricular craniopharyngiomas' differential diagnosis with different central nervous system tumors, such as low grade gliomas and germ cell tumors in the pediatric population, the frequent

occurrence of solid sellar/suprasellar lesions without intratumor cysts nor calcifications may pose some difficulties (4). In contrast, the ventricular involvement of CP-Vs, which most frequently originate from the suprasellar region, offers additional information to guide the pre-operative diagnosis, with distinct features as compared to other intraventricular tumors (37). In CP-Vs, pre-operative MRI assessment is also important to characterize the tumors' relationship with the hypothalamus and critical neurovascular structures, adapting surgical approaches and extent of tumor resection on each individual case.

In view of the complex anatomy of CP-Vs, surgical management requires multidisciplinary discussion between neurosurgery, otolaryngology, and radiation oncology (6, 9, 38). Cyst aspiration with biopsy and/or placement of Ommaya reservoir may be an option when tumor resection is deemed not feasible, with the purpose to confirm the diagnosis while reducing tumor's size and counteracting the continuous production of intra-cystic colloid fluid (39–41). Similarly, urgent shunting may be recommended in patients with obstruction of the ventricular system, aimed at promptly decreasing the intracranial pressure, stabilizing the patient, and planning the next treatment strategies (11, 42–44). When feasible, tumor resection remains the gold-standard also in CP-Vs to restore the visual function and/or the hypothalamic-pituitary axis, with GTR being preferred to reduce the risk of recurrence (4, 25). However, the high risk of post-surgical complications, primarily involving hypothalamic and/or pituitary stalk damage, may favor the completion of subtotal or partial tumor resection to reduce tumor size and ease adjuvant radiation planning (26, 45). Surgical access to CP-Vs somewhat differs from access to non-ventricular craniopharyngiomas, with the selection of the best corridors largely depending on surgeon's preference, tumor's epicenter, and extension within the ventricular system (38, 40, 46). In early series, only open surgical approaches were performed, in some cases reaching the target lesion through interhemispheric transcallosal corridors or transcortical-transventricular routes (29, 47). The trans-lamina terminalis route represented the preferred open surgical corridor, allowing easy access to the floor of the third ventricle, where the tumor is attached, through pterional or subfrontal approaches, with minimal risk of injuring the optic chiasm and the pituitary stalk (48–50). Of note, posterior fossa approaches, such as the retrosigmoid and the tonsillo-telovelar approaches, were performed in patients with fourth ventricle CP-Vs to access the cerebellopontine angle in the same fashion of other posterior fossa lesions (11, 18, 51). The introduction of endoscopic routes for sellar/suprasellar craniopharyngiomas and intraventricular tumors has led to its large adoption also for CP-Vs (52). Extended trans-sphenoidal and trans-ventricular endoscopic corridors offer adequate exposure of both suprasellar and intraventricular components of target CP-Vs, also allowing minimal brain retraction and wide angle of view (25, 38). However, the risks of inadequate control of adjacent neurovascular structures may pose some challenges in inexperienced hands, and should be carefully considered during pre-operative planning (46). Finally, combined open and endoscopic approaches constitute an additional option for large lesions, safely tackling intraventricular and extraventricular parts of the tumors to achieve maximal resection (40, 53).

The main therapeutic goals in CP-Vs focus on improving patients' functional status, prolonging local tumor control, and minimizing the risks of treatment-related complications. As found in this cohort, surgical resection led to high rates of symptom improvement (88%), with low rates of tumor recurrence (23.1%), comparable to the other non-ventricular craniopharyngiomas (54). However, both open and endoscopic tumor resection correlated with high rates of persistent post-surgical complications, mainly characterized by the disruption of hypothalamic-pituitary axis and similar to the adverse events after radiation treatment for other sellar/suprasellar lesions (55). The negative impact of these complications on patients' quality of life is partly limited by the optimal multidisciplinary medical management of hormone deficiencies available across most institutions (6). However, the narrow balance between surgical benefits and drawbacks deserves accurate consideration at pre-treatment stages. In terms of prognosis, CP-Vs show favorable OS rates, comparable to those of non-ventricular craniopharyngiomas (4, 9). Although pooled OS rates were significantly longer after endoscopic resection than those after open resection, we ascribe our results to the differences in years of publication in studies reporting the use of different routes, as open surgery was mostly performed in early series whereas endoscopic resection was preferred in more recent series (9, 29, 40, 47). These findings, coupled with the limited resources in terms of multidisciplinary patient management available in early series, may account for the shorter OS in patients who underwent open tumor resection.

Limitations. Our review has some limitations. All included studies were retrospective, likely exposed to selection bias and published within a 51-year time-period encompassing major changes in surgical protocols, which may have introduced some confounding variables into our analyses. The evaluation of baseline clinico-radiological presentation and post-treatment symptom improvement was subjective in most studies. Due to lack of granular clinical and imaging data found in the literature, we could not differentiate patients with infundibulo-tuberal and strictly intraventricular CP-Vs. Also, we could not analyze the impact of each variable on patient's functional and survival outcomes. Finally, as we included only patients with histologically confirmed diagnosis of CP-Vs, we could not compare the role of tumor resection *versus* stand-alone radiotherapy.

Conclusion

CP-Vs comprise heterogeneous and uncommon lesions with often debilitating clinical presentation and complex multidisciplinary management. Surgical resection, with or without ventricular shunting, allows prompt symptom improvement and favorable long-term tumor control, but causes high rates of post-treatment hypothalamic-pituitary axis disturbances. Several open and endoscopic surgical approaches are available, which should be pre-operatively considered and tailored to each patient to offer optimal tumor access while minimizing the risks of severe complications. Further molecular and genetic studies are warranted to accurately define the unique entities of CP-Vs, characterize their differences with the more common non-ventricular craniopharyngiomas, and, eventually, identify potential therapeutic targets.

Supplementary Material

Available at: https://www.dropbox.com/sh/3ro5iiq3216rnf3/AABghPV5HbXCPkCtHogb3svYa?dl=0

Conflicts of Interest

The Authors have no relevant financial or non-financial interests to disclose.

Authors' Contributions

Paolo Palmisciano: Conceptualization, methodology, data analysis, writing – original draft preparation; Kurtis Young: Resources, writing – reviewing and editing; Maya Ogasawara: Resources, writing – reviewing and editing; Omid Yousefi: Resources, writing – reviewing and editing; Christian Ogasawara: Resources, writing – reviewing and editing; Gianluca Ferini: Resources, writing – reviewing and editing; Othman Bin-Alamer: Resources, writing – reviewing and editing; Mayur Sharma: Resources, writing – reviewing and editing; Giuseppe E. Umana: Resources, writing – reviewing and editing; Kenny Yu: Resources, writing – reviewing and editing; Aaron A. Cohen-Gadol: Resources, writing – reviewing and editing; Tarek Y. El Ahmadieh: Resources, writing – reviewing and editing; Ali S. Haider: Methodology, resources, writing – reviewing and editing, supervision.

References

1 Zacharia BE, Bruce SS, Goldstein H, Malone HR, Neugut AI and Bruce JN: Incidence, treatment and survival of patients with craniopharyngioma in the surveillance, epidemiology and end results program. Neuro Oncol *14(8)*: 1070-1078, 2012. PMID: 22735773. DOI: 10.1093/neuonc/nos142

2 Nielsen EH, Feldt-Rasmussen U, Poulsgaard L, Kristensen LO, Astrup J, Jørgensen JO, Bjerre P, Andersen M, Andersen C, Jørgensen J, Lindholm J and Laurberg P: Incidence of craniopharyngioma in Denmark (n=189) and estimated world incidence of craniopharyngioma in children and adults. J Neurooncol *104(3)*: 755-763, 2011. PMID: 21336771. DOI: 10.1007/s11060-011-0540-6

3 Atwell W: The development of the hypophysis cerebri in man, with special reference to the pars tuberalis. American Journal of Anatomy *37(1)*: 159-193, 2021. DOI: 10.1002/aja.1000370107

4 Müller HL, Merchant TE, Warmuth-Metz M, Martinez-Barbera JP and Puget S: Craniopharyngioma. Nat Rev Dis Primers *5(1)*: 75, 2019. PMID: 31699993. DOI: 10.1038/s41572-019-0125-9

5 Hoffmann A, Boekhoff S, Gebhardt U, Sterkenburg AS, Daubenbüchel AM, Eveslage M and Müller HL: History before diagnosis in childhood craniopharyngioma: associations with initial presentation and long-term prognosis. Eur J Endocrinol *173(6)*: 853-862, 2015. PMID: 26392473. DOI: 10.1530/EJE-15-0709

6 Müller HL, Merchant TE, Puget S and Martinez-Barbera JP: New outlook on the diagnosis, treatment and follow-up of childhood-onset craniopharyngioma. Nat Rev Endocrinol *13(5)*: 299-312, 2017. PMID: 28155902. DOI: 10.1038/nrendo.2016.217

7 Pascual JM, González-Llanos F, Barrios L and Roda JM: Intraventricular craniopharyngiomas: topographical classification and surgical approach selection based on an extensive overview. Acta Neurochir (Wien) *146(8)*: 785-802, 2004. PMID: 15254801. DOI: 10.1007/s00701-004-0295-3

8 Pascual JM, Prieto R and Carrasco R: Infundibulo-tuberal or not strictly intraventricular craniopharyngioma: evidence for a major topographical category. Acta Neurochir (Wien) *153(12)*: 2403-25; discussion 2426, 2011. PMID: 21918833. DOI: 10.1007/s00701-011-1149-4

9 Prieto R, Barrios L and Pascual JM: Strictly third ventricle craniopharyngiomas: pathological verification, anatomo-clinical characterization and surgical results from a comprehensive overview of 245 cases. Neurosurg Rev *45(1)*: 375-394, 2022. PMID: 34448081. DOI: 10.1007/s10143-021-01615-0

10 Mishra SS, Behera SK, Senapati SB and Panigrahi S: Cystic craniopharyngioma of lateral ventricle with small stalk in suprasellar cistern: a rare case. Neurol India *61(4)*: 434-436, 2013. PMID: 24005746. DOI: 10.4103/0028-3886.117599

11 Sharma M, Mally R, Velho V and Hrushikesh K: Primary isolated cerebellopontine angle papillary craniopharyngioma. Neurol India *60(4)*: 438-439, 2012. PMID: 22954990. DOI: 10.4103/0028-3886.100727

12 Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P and Moher D: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ *372*: n71, 2021. PMID: 33782057. DOI: 10.1136/bmj.n71

13 Howick J, Chalmers I, Glasziou P, Greenhalgh T, Heneghan C, Liberati A, Moschetti I, Phillips B and Thornton H: Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (Background Document). Oxford Cent Evidence-Based Med, 2011. Available at: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence [Last accessed on July 12, 2022]

14 Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF and PRISMA-IPD Development Group: Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. JAMA *313(16)*: 1657-1665, 2015. PMID: 25919529. DOI: 10.1001/jama.2015.3656

15 Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetc R, Currie M, Lisy K, Qureshi R, Mattis P and Mu P: Chapter 7: Systematic Reviews of Etiology and Risk. JBI Manual for Evidence Synthesis, 2020. DOI: 10.46658/JBIMES-20-08

16 Xu JG, You C, Cai BW, Jiang S, Sun H, Guo FY, Yang YB and Wu B: Microsurgical resection of craniopharyngioma of the third ventricle via an improved transventricular approach. Chin Med J (Engl) *118(10)*: 806-811, 2005. PMID: 15989759.

17 Shah GB, Bhaduri AS and Misra BK: Ectopic craniopharyngioma of the fourth ventricle: case report. Surg Neurol *68(1)*: 96-98, 2007. PMID: 17586238. DOI: 10.1016/j.surneu.2006.11.073

18 Singh P, Sarkari A, Sarat Chandra P, Mahapatra AK, Sharma BS and Gurjar HK: Giant craniopharyngioma presenting as a cerebellopontine angle tumour. Pediatr Neurosurg *48(2)*: 131-132, 2012. PMID: 23128556. DOI: 10.1159/000343483

19 Pena AH, Chaudhry A, Seidman RJ, Peyster R and Bangiyev L: Ectopic craniopharyngioma of the fourth ventricle in a patient with Gardner syndrome. Clin Imaging *40(2)*: 232-236, 2016. PMID: 26995577. DOI: 10.1016/j.clinimag.2015.11.005

20 Algahtani AY, Algahtani HA, Jamjoom AB, Samkari AM and Marzuk YI: *De novo* craniopharyngioma of the fourth ventricle: Case report and review of literature. Asian J Neurosurg *13(1)*: 62-65, 2018. PMID: 29492123. DOI: 10.4103/1793-5482.185063

21 Sharma R, Davis C and Lynch P: To the editor. Surgical Neurology *42(6)*: 551-552, 2019. DOI: 10.1016/0090-3019(94)90094-9

22 Davies MJ, King TT, Metcalfe KA and Monson JP: Intraventricular craniopharyngioma: a long-term follow-up of six cases. Br J Neurosurg *11(6)*: 533-541, 1997. PMID: 11013625. DOI: 10.1080/02688699745691

23 Pascual JM, Prieto R, Navas M and Carrasco R: Conquest of third ventricle craniopharyngiomas. J Neurosurg *112(5)*: 1156-61; author reply 1161, 2010. PMID: 20345221. DOI: 10.3171/2009.8.JNS091094

24 Ciric IS and Cozzens JW: Craniopharyngiomas: transsphenoidal method of approach—for the virtuoso only? Clin Neurosurg *27*: 169-187, 1980. PMID: 7273552.

25 Forbes JA, Ordóñez-Rubiano EG, Tomasiewicz HC, Banu MA, Younus I, Dobri GA, Phillips CD, Kacker A, Cisse B, Anand VK and Schwartz TH: Endonasal endoscopic transsphenoidal resection of intrinsic third ventricular craniopharyngioma: surgical results. J Neurosurg : 1-11, 2018. PMID: 30497140. DOI: 10.3171/2018.5.JNS18198

26 Algattas H, Setty P, Goldschmidt E, Wang EW, Tyler-Kabara EC, Snyderman CH and Gardner PA: Endoscopic endonasal approach for craniopharyngiomas with intraventricular extension: Case series, long-term outcomes, and review. World Neurosurg *144*: e447-e459, 2020. PMID: 32890848. DOI: 10.1016/j.wneu.2020.08.184

27 Young SC, Zimmerman RA, Nowell MA, Bilaniuk LT, Hackney DB, Grossman RI and Goldberg HI: Giant cystic craniopharyngiomas. Neuroradiology *29(5)*: 468-473, 1987. PMID: 3317110. DOI: 10.1007/BF00341745

28 Yang Y, Shrestha D, Shi XE, Zhou Z, Qi X and Qian H: Ectopic recurrence of craniopharyngioma: Reporting three new cases. Br J Neurosurg *29(2)*: 295-297, 2015. PMID: 25311042. DOI: 10.3109/02688697.2014.967751

29 Long DM and Chou SN: Transcallosal removal of craniopharyngiomas within the third ventricle. J Neurosurg *39(5)*: 563-567, 1973. PMID: 4542715. DOI: 10.3171/jns.1973.39.5.0563

30 Gabel BC, Cleary DR, Martin JR, Khan U, Snyder V and Sang UH: Unusual and rare locations for craniopharyngiomas: clinical significance and review of the literature. World Neurosurg *98*: 381-387, 2017. PMID: 27908738. DOI: 10.1016/j.wneu.2016.10.134

31 Martinez-Barbera JP and Andoniadou CL: Concise review: Paracrine role of stem cells in pituitary tumors: a focus on adamantinomatous craniopharyngioma. Stem Cells *34(2)*: 268-276, 2016. PMID: 26763580. DOI: 10.1002/stem.2267

32 Martinez-Gutierrez JC, D'Andrea MR, Cahill DP, Santagata S, Barker FG 2nd and Brastianos PK: Diagnosis and management of craniopharyngiomas in the era of genomics and targeted therapy. Neurosurg Focus *41(6)*: E2, 2016. PMID: 27903124. DOI: 10.3171/2016.9.FOCUS16325

33 Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F and Bruner JM: The descriptive epidemiology of craniopharyngioma. J Neurosurg *89(4)*: 547-551, 1998. PMID: 9761047. DOI: 10.3171/jns.1998.89.4.0547

34 Pascual JM, Prieto R, Castro-Dufourny I, Mongardi L, Rosdolsky M, Strauss S, Carrasco R and Barrios L: Craniopharyngiomas primarily involving the hypothalamus: a model of neurosurgical lesions to elucidate the neurobiological basis of psychiatric disorders. World Neurosurg *120*: e1245-e1278, 2018. PMID: 30240857. DOI: 10.1016/j.wneu.2018.09.053

35 Cushing H: The Pituitary Body and its Disorders. Clinical states produced by disorders of the hypophysis cerebri. Philadelphia & London, JB Lippinc., 1912.

36 Rossi A, Cama A, Consales A, Gandolfo C, Garrè ML, Milanaccio C, Pavanello M, Piatelli G, Ravegnani M and Tortori-Donati P: Neuroimaging of pediatric craniopharyngiomas: a pictorial essay. J Pediatr Endocrinol Metab *19(Suppl 1)*: 299-319, 2006. PMID: 16700305.

37 Muly S, Liu S, Lee R, Nicolaou S, Rojas R and Khosa F: MRI of intracranial intraventricular lesions. Clin Imaging *52*: 226-239, 2018. PMID: 30138862. DOI: 10.1016/j.clinimag.2018.07.021

38 Almeida JP, Kalyvas A, Mohan N, Oswari S, Takami H, Velasquez C, Asha M, Zadeh G and Gentili F: Current results of surgical treatment of craniopharyngiomas: the impact of endoscopic endonasal approaches. World Neurosurg *142*: 582-592, 2020. PMID: 32987614. DOI: 10.1016/j.wneu.2020.05.174

39 Shoubash LI, El Refaee E, Al Menabbawy A, Refaat MI, Fathalla H and Schroeder HWS: Endoscopic transcortical-transventricular approach in treating third ventricular craniopharyngiomas-case series with technical note and literature review. Oper Neurosurg (Hagerstown) *22(4)*: 192-200, 2022. PMID: 35147594. DOI: 10.1227/ONS.0000000000000114

40 Deopujari C, Behari S, Shroff K, Kumar A, Thombre B, Karmarkar V and Mohanty C: Intraventricular craniopharyngiomas-overcoming their relative inaccessibility: institutional experience with a review of literature. Front Neurol *12*: 755784, 2021. PMID: 34867741. DOI: 10.3389/fneur.2021.755784

41 Shukla D: Transcortical transventricular endoscopic approach and ommaya reservoir placement for cystic craniopharyngioma. Pediatr Neurosurg *50(5)*: 291-294, 2015. PMID: 26159247. DOI: 10.1159/000433605

42 Fukushima T, Hirakawa K, Kimura M and Tomonaga M: Intraventricular craniopharyngioma: its characteristics in magnetic resonance imaging and successful total removal. Surg Neurol *33(1)*: 22-27, 1990. PMID: 2405528. DOI: 10.1016/0090-3019(90)90220-j

43 Matthews FD: Intraventricular craniopharyngioma. AJNR Am J Neuroradiol *4(4)*: 984-985, 1983. PMID: 6410885.
44 Mori K, Handa H, Murata T, Ishikawa M, Takeuchi J and Osaka K: Craniopharyngiomas with unusual topography and associated with vascular pathology. Acta Neurochir (Wien) *53(1-2)*: 53-68, 1980. PMID: 7435282. DOI: 10.1007/BF02074521
45 Elkheshin S, Aziz L and Bebars M: Endoscopic trans-ventricular resection of cystic craniopharyngioma in adults associated with hydrocephalus, an alternative minimally invasive approach. Interdisciplinary Neurosurgery *28*: 101449, 2022. DOI: 10.1016/j.inat.2021.101449
46 Hardesty DA, Montaser AS, Beer-Furlan A, Carrau RL and Prevedello DM: Limits of endoscopic endonasal surgery for III ventricle craniopharyngiomas. J Neurosurg Sci *62(3)*: 310-321, 2018. PMID: 29378389. DOI: 10.23736/S0390-5616.18.04331-X
47 Ghatak NR, Hirano A and Zimmerman HM: Ultrastructure of a craniopharyngioma. Cancer *27(6)*: 1465-1475, 1971. PMID: 4103497. DOI: 10.1002/1097-0142(197106)27:6<1465::aid-cncr2820270629>3.0.co;2-7
48 Maira G, Anile C, Colosimo C and Cabezas D: Craniopharyngiomas of the third ventricle: trans-lamina terminalis approach. Neurosurgery *47(4)*: 857-63; discussion 863-5, 2000. PMID: 11014425. DOI: 10.1097/00006123-200010000-00014
49 Sohma T, Takigami M, Sasamori T, Okuboa A, Momota H and Ogawa Y: Intra-third ventricular craniopharyngiomas: imaging characteristics, histopathology and successful trans-lamina terminalis approach. International Congress Series *1259*: 111-117, 2019. DOI: 10.1016/S0531-5131(03)01404-3
50 King TT: Removal of intraventricular craniopharyngiomas through the lamina terminalis. Acta Neurochir (Wien) *45(3-4)*: 277-286, 1979. PMID: 425858. DOI: 10.1007/BF01769141
51 Palmisciano P, Haider AS, Sabahi M, Nwagwu CD, Bin Alamer O, Scalia G, Umana GE, Cohen-Gadol AA, El Ahmadieh TY, Yu K and Pathmanaban ON: Primary skull base chondrosarcomas: a systematic review. Cancers (Basel) *13(23)*: 5960, 2021. PMID: 34885071. DOI: 10.3390/cancers13235960
52 Cavallo LM, Di Somma A, de Notaris M, Prats-Galino A, Aydin S, Catapano G, Solari D, de Divitiis O, Somma T and Cappabianca P: Extended endoscopic endonasal approach to the third ventricle: multimodal anatomical study with surgical implications. World Neurosurg *84(2)*: 267-278, 2015. PMID: 25827043. DOI: 10.1016/j.wneu.2015.03.007
53 Renfrow JJ, Greeneway GP, Carter L and Couture DE: Intraventricular recurrence of a craniopharyngioma: case report. J Neurosurg Pediatr *22(4)*: 393-396, 2018. PMID: 29957141. DOI: 10.3171/2018.4.PEDS18112
54 Ordóñez-Rubiano EG, Forbes JA, Morgenstern PF, Arko L, Dobri GA, Greenfield JP, Souweidane MM, Tsiouris AJ, Anand VK, Kacker A and Schwartz TH: Preserve or sacrifice the stalk? Endocrinological outcomes, extent of resection, and recurrence rates following endoscopic endonasal resection of craniopharyngiomas. J Neurosurg: 1-9, 2018. PMID: 30497145. DOI: 10.3171/2018.6.JNS18901
55 Palmisciano P, Ogasawara C, Ogasawara M, Ferini G, Scalia G, Haider AS, Bin Alamer O, Salvati M and Umana GE: Endocrine disorders after primary gamma knife radiosurgery for pituitary adenomas: A systematic review and meta-analysis. Pituitary *25(3)*: 404-419, 2022. PMID: 35349010. DOI: 10.1007/s11102-022-01219-x

Received July 1, 2022
Revised July 12, 2022
Accepted July 13, 2022